PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

BAKER, Suzanne, Jane
GlaxoSmithKline
Corporate Intellectual Property CN9
980 Great West Road
Brentford, Middlesex TW8 9GS
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	20.12.2004
Applicant's or agent's file reference: SJB/PG5042	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/13800	04.12.2003	06.12.2002

Applicant
GLAXO GROUP LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Geier, A Tel. +49 30 25901-706

Form PCT/IPEA/416 (January 2004)

Express Mail Label:
EV330919360US

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SJB/PG5042	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13800	International filing date *(day/month/year)* 04.12.2003	Priority date *(day/month/year)* 06.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D409/12		
Applicant GLAXO GROUP LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 16.06.2004	Date of completion of this report 20.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized Officer Frelon, D Telephone No. +49 30 25901-312

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13800

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-20 as originally filed

Claims, Numbers

1-18 as originally filed

Drawings, Sheets

1-2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 18

   because:

   ☒ the said international application, or the said claims Nos. 18 with regards to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 18 with regards to industrial applicability

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-18
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claim 18 is directed to methods for treatment of the human or animal body by surgery or therapy as well as diagnostic methods. It relates to a subject-matter considered by this authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claims (Article 34 (4) (a)(i) PCT).

Under the terms of Rule 39.1(iv) PCT, the ISA was not required to carry out a search of such claims, but as indicated in the ISR, the search was carried out and based on the alleged effects of the compounds. Similarly, the IPEA (which is the ISA) is not required to carry out an International preliminary examination of such claims, but as for the ISR, the IPER will be based on the alleged effects of the compounds (Rule 67.1 (iv) PCT).

Re Item V

1. **Cited documents**

D1: WO 02/100830 A (SHAH GITA PUNJABHAI ; YOUNG ROBERT JOHN (GB); SENGER STEFAN (GB); CHAN) 19 December 2002 - intermediate document
D2: WO 02/100886 A (SHAH GITA PUNJABHAI ; YOUNG ROBERT JOHN (GB); SENGER STEFAN (GB); CHAN) 19 December 2002 - intermediate document

2. **Novelty**

The intermediate documents D1 and D2 are relevant for the purposes of Rules 33.1 c, 64.3 and 70.10 PCT, but since the priority documents are not available at the time of establishing the written opinion, they are cannot be taken into account. It is based on the assumption that all claims enjoy priority rights from the filing date of the priority document(s). If it later turns out that this assumption is not correct, the intermediate document in the International Search Report (ISR) could become relevant in order to assess whether the claims satisfy the criteria set forth in Article 33(1) PCT.
If the priority date is not valid for the complete claimed subject-matter, this document may

become relevant prior art in a possible regional/national phase.

Note that the compound the formula of which is given in the main claim is disclosed in D1 (example 61) and D2 (example 386), in particular as a "white solid".
No crystalline form appears to have been specifically previously disclosed.

The applicant has shown that the compound in question can be crystallized by using a given method. It is usually known by the skilled person that crystallizable compounds may form various crystal types depending on the methods of obtention (the "form" needle- or lath-shape- is a macroscopic aspect which is not always necessarily -unless contrarily proved- characteristic of a crystal type). The crystal obtained is therefore not "any" crystal but a particular type defined and recognized by specific physical characteristics as shown by an X-ray powder diffraction pattern in particular processing conditions, especially the apparatus.

These conditions belong to a proper crystal definition and should be supplemented in the main claim. It is additionally mentioned that the term "substantially" as it affects the essential criterion of the claimed subject-matter, *i.e.* the crystalline form, requires to be unambiguous. A clear support exists in the description.

3. Inventive step

3.1 The problem underlying the present application was to provide a crystalline form of a Factor Xa inhibiting agent claimed in an intermediate patent application.

3.2 It belongs to the usual routine (general knowledge) of the skilled person to look for and obtain crystalline forms of known compounds, especially medicaments, because advantages can be expected for their storage or their dispensing (biological availibility, medicine formulation, etc).

Nothing is said in the prior art that any prejudice would have prevent the skilled person from making a crystal starting from a compound known in solid form. Neither is said which particular and surprising effect (possibly an unexpected advantage) is brought by the presently claimed unspecific "substantially crystalline form". On the contrary, the

specification of the crystal by its physico-chemical characteristics would allow to identify the product unambiguously in such a way that it could not be considered as directly derivable from the teaching of the general kowledge of skilled persons. These so specified distinguishing features constitute in fact the unexpected effect required for the acknowledgment of an inventive step.